

Pharmacotherapy of Depressed Children and Adolescents: Current Issues and Potential Directions

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The recent deliberations by the U.S. Food and Drug Administration (FDA) regarding the relationship between antidepressants and suicidality in children have incited debates about the safety of these medications for the treatment of pediatric depression. In light of these events, this review discusses four issues pertaining to pharmacotherapy for pediatric depression. First, we summarize pertinent data from randomized controlled trials of antidepressants for pediatric depression. These data provide strong support for fluoxetine and modest support for the other antidepressants. Second, we examine the outcome of the FDA meta-analysis of the data on antidepressant-induced suicidality, with specific emphasis on the methodological limitations of this analysis. Third, we consider the collective implications of the antidepressant efficacy and suicidality data on clinical practice. Specifically, we present several compelling arguments that justify the continued use of antidepressants for pediatric depression, despite the inherent limitations of these medications. Finally, we review several pathophysiological factors that might provide insights into treatment response and impact the design of future pharmacotherapy studies of depression. These factors relate to diagnostic heterogeneity, developmental consistency, and psychobiology. Potentially novel pharmacotherapies are also discussed.

Key Words: Major depression, pediatric, antidepressants, clinical trials

Major depression is a common condition that affects approximately 5% of children and adolescents (Shaffer et al 1996). Given the significant acute and chronic burden associated with this disorder, developing effective treatments is of paramount importance.

During the past 2 decades, the availability of selective serotonin reuptake inhibitors (SSRIs) has transformed the treatment of pediatric depression (major depressive disorder, MDD). Whereas tricyclic antidepressants (TCAs) were once considered a primary treatment for this disorder, SSRIs and other newer antidepressants (i.e., bupropion, mirtazapine, nefazodone, venlafaxine) have become the most popular therapies. In 2002, U.S. physicians wrote nearly 11 million prescriptions for SSRIs and other non-TCA antidepressants for youth aged less than 17 years (Hampton 2004). Far fewer prescriptions were written for TCAs. Factors contributing to this shift in prescribing practices include an accumulation of data indicating that TCAs are neither safe nor efficacious (Hazell et al 1995; Varley 2001) and the excellent tolerability profile of the SSRIs compared with TCAs (Barbey and Roose 1998).

Widespread use of SSRIs, however, might change in the wake of the “black box” warning issued by the U.S. Food and Drug Administration (FDA) in October 2004 which reports an association between antidepressants and increased risk of suicidality. This warning has ignited serious debate among clinicians, researchers, and the public at large regarding the efficacy and safety of antidepressants. The field of child psychiatry has therefore reached a crossroads, whereby consensus is needed regarding the most suitable treatments for MDD. Furthermore, this debate highlights our limited therapeutic armamentarium and stresses the need for placing high priority on research pursuing novel pharmacotherapies.

During the past 2 years, many critical reviews of the pediatric antidepressant data have emerged in the literature (Cheung et al 2005; Courtney 2004; Emslie et al 2005; Jureidini et al 2004; Licinio and Wong 2005; U.S. Food and Drug Administration 2004a; Wagner 2005; Whittington et al 2004). These reviews summarize data from the 24 published and unpublished pediatric randomized, controlled trials (RCTs) that were examined at the September 2004 FDA meeting. Those studies consisted of 18 antidepressant trials for MDD (12 of SSRIs, 3 of venlafaxine, 2 of nefazodone, and 1 of mirtazapine), 3 SSRI trials for obsessive-compulsive disorder (OCD), 1 venlafaxine trial for generalized anxiety disorder, 1 paroxetine trial for social anxiety disorder, and 1 bupropion trial for attention-deficit/hyperactivity disorder. Two additional studies of MDD, one for citalopram and a second for escitalopram, were reviewed in less detail.

The present review differs from prior reports on this topic in two noteworthy ways. First, in contrast to prior reports which are more broadly focused, we summarize major themes pertaining exclusively to the SSRI efficacy data for pediatric MDD, with particular emphasis on their inconsistencies, limitations, and relation to treatment data pertaining to other adult and child emotional disorders. On the basis of these efficacy data, as well as the antidepressant-related suicidality data, we provide convincing arguments in support of antidepressant use for pediatric MDD. Second, unlike prior reports, we include a discussion of the developmental psychobiological factors that might underlie treatment response in pediatric MDD. Although very little research has been conducted in this area, we present relevant pathophysiological data from adult and translational studies that might provide insights regarding future studies of pathophysiology and treatment response in children. We also discuss ethical issues pertaining to research on new medications for pediatric depression and provide examples of potentially novel treatments that are currently under investigation for adult depression.

Antidepressant Efficacy Data

The past decade has witnessed a rapid accumulation of RCTs investigating antidepressant efficacy for various childhood disorders. One of the most influential factors stimulating this increase was the FDA Modernization Act of 1997. This Act created opportunities for pharmaceutical companies to conduct clinical trials of medications that the FDA deemed a priority. In exchange for conducting these trials, pharmaceutical companies were

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Table 1. Published Randomized Placebo-Controlled Trials of SSRIs of Pediatric Depression

Study	Funding Source	Study Design			Response Rates (%)	
		Sites	Drug (length in weeks)	Outcome Measures	Drug	Placebo
Emslie et al (1997)	NIMH	Single	Fluoxetine (8)	CGI-I (at exit)	56	33
				CGI-I (at completion)	74	58 ^a
Emslie et al (2002)	Eli Lilly	Multi	Fluoxetine (9)	CDRS-R	65	53 ^b
TADS Group (2004) ^c	NIMH	Multi	Fluoxetine (12)	CGI-I	61	35
Keller et al (2001)	GlaxoSmith-Kline	Multi	Paroxetine (8)	HAM-D	63	46
				CGI-I	66	48
Wagner et al (2003)	Pfizer	Multi	Sertraline (10)	CDRS-R	69	59
Wagner et al (2004b)	Forest	Multi	Citalopram (8)	CDRS-R	36	24

SSRIs, selective serotonin reuptake inhibitors; NIMH, National Institute of Mental Health; CGI-I, Clinical Global Impression–Improvement; CDRS-R, Children’s Depression Rating Scale–Revised; TADS, Treatment for Adolescents with Depression Study; HAM-D, Hamilton Rating Scale for Depression.

^aNo significant difference in response rates at study completion.

^bNo significant difference in response rates were found; however, significant group differences in the mean CDRS score were present.

^cTADS is the only comparative study of cognitive behavioral therapy (CBT) and medication. The response rates for the CBT monotherapy and combined drug/CBT conditions were 43% and 71%, respectively.

granted an additional 6 months of patent exclusivity for the study medication. This Act had a profound impact on child psychiatry, given the high prevalence of pediatric psychopathology and the paucity of data on psychotropic medication efficacy. Of note, disclosure of data from RCTs to the public or scientific community was not a requirement of the Act. As such, the FDA review of the antidepressant data in October 2004 was precipitated when data from unpublished studies reached the FDA through relatively circuitous routes.

This section summarizes the main conclusions from RCTs of SSRIs for pediatric MDD. Table 1 summarizes the findings of published studies. Two important aspects of the efficacy data are discussed. First, we posit several explanations that might contribute to inconsistencies in these data. Second, given the significant overlap between anxiety and depressive disorders, we call attention to differences in SSRI efficacy data between pediatric MDD, adult MDD, and pediatric anxiety disorders.

Findings from Randomized Controlled Trials

Data from three published RCTs demonstrate efficacy of fluoxetine, although a fourth study found no benefits. An initial study from Emslie et al (1997) in 96 depressed youth and a second study from Emslie et al (2002) in 219 depressed youth both found significant differences between fluoxetine and placebo on the primary outcome variables. Similarly, the Treatment of Adolescent Depression Study (TADS; 2004) compared the response to fluoxetine, placebo, cognitive behavioral psychotherapy (CBT), and combined CBT–fluoxetine treatment in 439 adolescents with MDD. In terms of the response rates on the Clinical Global Improvement Scale, the results showed that the CBT–fluoxetine combination (71% response rate) was superior to monotherapy with fluoxetine (61%), CBT (43%), or placebo (35%). Furthermore, across monotherapy conditions, fluoxetine was superior to CBT and placebo. These response rates might have been affected by an expectancy bias, because youth randomized to the combined treatment group were not blind to their medication status. Finally, a fourth fluoxetine–MDD study found no differences on any outcome measure in 40 depressed adolescents randomized to fluoxetine or placebo (Simeon et al 1990). Because the sample was small ($n = 30$) and the methods were only briefly described, this study was not included in Table 1.

Efficacy data on the remaining SSRIs are less consistent than the data on fluoxetine. In terms of citalopram, one study provides reasonably clear evidence of efficacy (Wagner et al 2004b);

however, a second, unpublished study of citalopram (U.S. Food and Drug Administration 2004a), as well as a third, unpublished study of escitalopram (Wagner et al, unpublished data), found no group differences. With regard to sertraline, two studies reported insignificant benefits of sertraline relative to placebo for MDD (Wagner et al 2003). Combining the data from these two studies yielded a statistically significant advantage for sertraline, but the magnitude of this effect was small and of questionable clinical significance (McClure et al 2004). Last, one study of paroxetine demonstrated relatively weak evidence of efficacy (Keller et al 2001), whereas two unpublished studies failed to detect group differences (Emslie et al 2004; Milin et al, unpublished data).

In summary, two main conclusions emerge from the efficacy data. First, there is reasonably strong evidence for efficacy of fluoxetine, such that fluoxetine can be considered a first-line treatment for pediatric MDD. Second, efficacy of the remaining SSRIs is modest at best. Nevertheless, given cross-study methodological differences, lack of more robust support for these other agents does not necessarily correspond to lack of efficacy.

Factors Contributing to Differential Efficacy Data

The distinct advantage of fluoxetine over other SSRIs in pediatric MDD seems surprising in light of other adult and child treatment data indicating comparable efficacy of SSRIs for depression and anxiety. The majority of adult MDD and anxiety treatment studies do not suggest a preferential advantage of one SSRI over another (Vaswani et al 2003). Similarly, studies of pediatric OCD and particularly non-OCD anxiety disorders demonstrate significant benefits of various SSRIs (Birmaher et al 2003; Riddle et al 2001; Research Unit on Pediatric Psychopharmacology Anxiety Study Group 2001; Wagner et al 2004a).

The most likely explanation for the inconsistent efficacy data in pediatric MDD relates to cross-study methodological differences for individual SSRI trials, notably differences in subject selection and assessment methodology. Ascertaining a valid MDD diagnosis and tracking treatment response requires extensive training to establish reliability among investigators at a limited number of sites. The three positive fluoxetine trials carefully characterized depressed subjects with relatively rigorous methods, whereas studies of other agents demonstrated less evidence of methodological rigor. For example, the two studies of sertraline did not establish interrater reliability on the assessment of primary endpoints (Wagner et al 2003).

A second potential explanation for these inconsistencies

relates to differences in the pharmacological properties of individual SSRIs. First, the differential half-lives of SSRIs might influence medication–placebo differences if subjects exhibit poor compliance. Group differences might be less profound with fluoxetine, owing to its long half-life (Wilens et al 2002). This explanation, however, does not account for the comparable efficacy of both short- and long-half-life SSRIs for pediatric anxiety disorders. Furthermore, no data suggest that poor compliance is more characteristic of pediatric MDD than anxiety. The second difference might relate to the secondary actions of fluoxetine that are not shared by other SSRIs (Shelton 2000), but this explanation also seems unlikely given data on the consistency of SSRI response in adult MDD and pediatric anxiety.

Limitations and Future Studies

Limitations of the current RCTs might provide directions for refining the methods of future studies. Methodological guidelines for future studies are outlined in Table 2. The first limitation relates to the high and variable placebo response rate, a finding also seen in adult MDD (Schatzberg and Kraemer 2000; Trivedi and Rush 1994). Various strategies have been used to reduce the high placebo response rate, all with modest success. For example, relatively high placebo response rates have occurred in studies using prerandomization procedures to eliminate individuals responsive to supportive psychoeducational interventions or studies using an open placebo trial (Emslie et al 1997, 2002; Geller et al 1992; Research Unit on Pediatric Psychopharmacology Anxiety Study Group 2001). Clinical trials in adult MDD suggest that alternative study designs might be more successful in reducing the placebo response. For example, designs using an initial open treatment phase, followed by randomization of responders to either placebo substitution or continued antidepressant treatment, are more beneficial than traditional antidepressant–placebo parallel group designs (U.S. Food and Drug Administration 2004b). Other limitations include the relatively low rates of remission for any SSRI and the lack of group

differences in self-report measures, which might reflect clinician bias (Lambert et al 1986). Finally, there is a dearth of long-term medication studies and comparative efficacy studies of medication and psychotherapy. These studies are necessary to establish systematic clinical guidelines that dictate the course of treatment when first-line treatments fail.

Antidepressants and Suicidal Thoughts or Behavior

In October 2004, the FDA issued a “black box” warning alerting physicians and the public about the association between pediatric antidepressant use and increased risk of suicidal thoughts and behavior. This warning was based on the outcome of the FDA advisory committee’s review of the meta-analysis of data from 24 acute placebo-controlled trials involving more than 4400 children and adolescents with a diagnosis of MDD, anxiety, or other psychiatric disorders. The results revealed that 78 patients reported suicidal thinking or behavior. The average risk of these events was 4% in the medication group and 2% in the placebo group. No completed suicides occurred in these trials. Moreover, the increase in suicidality represented a small risk in a relatively small sample of exposed youth. Furthermore, although the aggregate results showed statistically significant group differences, no single trial demonstrated this finding. A detailed account of these events, as well as the meta-analysis data, can be found in Licinio and Wong (2005) and on the FDA web site (U.S. Food and Drug Administration 2004a), respectively.

Although the FDA panel endorsed the risk of antidepressant-related suicidality, the precise nature of this relationship is poorly understood owing to two limitations in the data. First, researchers conducting clinical trials of antidepressant efficacy collected few details for some patients regarding the nature of the particular events involving suicidal thoughts or behavior. This might have compromised the degree of accuracy in classifying each event as a “true” instance of suicidal behavior, as opposed to a general increase in irritability or impulsive behavior. To maximize accuracy in classification, the FDA commissioned a review by an expert panel to examine individual cases of suicidal events; however, given the limitations in the raw data, even this external review was seen as suboptimal by members of the FDA committee.

Second, considerable heterogeneity was present across RCTs in terms of the antidepressant studied, patient characteristics, number of sites, and data collection procedures. Moreover, variability emerged across studies and even across measures within the same study for the risk estimates of associations between antidepressant versus placebo and suicidal thoughts or behavior. Limited statistical power precluded detection of even moderately large sources of variability, however, owing to the low rates of suicidal thoughts or behaviors across the different trials for the various agents (i.e., 78 out of more than 4400 patients). The analyses therefore failed to identify any specific factor that contributed to the cross-study variability in the point estimates. As such, the “black box” warning was universally applied to all potential agents, including those that did not yield a single episode of suicidality, simply because it could not be determined whether the absence of such events was a chance finding.

Treatment Recommendations

Concerns about the use of antidepressants for pediatric MDD are understandable given the constraints regarding their efficacy and safety. Some critical reviewers, however, continue to main-

Table 2. Recommendations for Future Randomized Controlled Trials of Pediatric Depression

- 1) Types of Future Studies
 - a. Short-term studies examining efficacy of current and newer antidepressants using more rigorous assessment methods
 - b. Longitudinal studies investigating the efficacy and adverse effects of extended use of antidepressants (i.e., beyond 12–16 weeks)
 - c. Comparative studies of antidepressants and psychotherapy (combination vs. monotherapy)
- 2) Strategies to Improve Study Design
 - a. Inclusion of fewer sites
 - b. Implementation of consistent training procedures and demonstration of reliability across sites
 - c. Prerandomization procedures to reduce placebo response rates (e.g., open treatment with an antidepressant followed by blind randomization to either drug or placebo)
 - d. Systematic methods for detecting adverse events
- 3) Strategies to Obtain More Clinically or Pathophysiologically Homogeneous Groups
 - a. Inclusion of children with particular depressive subtypes
 - b. Inclusion of children with similar course of illness (e.g., early onset, chronic, recurrent)
 - c. Inclusion of children with similar ages
 - d. Inclusion of children with similar neural or behavioral responses
- 4) Consideration of Novel Experimental Therapies in Children with Treatment-Resistant Depression

tain the view that SSRIs, as a group, are reasonable treatment options for pediatric MDD (Brent 2004; Wagner 2005).

Four sets of findings provide strong support for antidepressant treatment in children and adolescents. First, longitudinal data demonstrate that pediatric MDD is associated with significant morbidity and mortality (Birmaher et al 2002). Moreover, the majority of adolescents who commit suicide suffer from a mood disorder; most of these adolescents were not receiving any form of treatment (Houston et al 2001). Thus, antidepressant treatment can be seen as justified given the potential risks of not treating the illness.

Second, epidemiologic data indicate that the pediatric suicide rate has decreased throughout the late 20th century in the United States (Brent 2004) and that this trend occurred during a time of increasing antidepressant use. Olfson et al (2003) examined the temporal relationship between changes in prescription rates and completed suicide rates in 10–19-year-old children and adolescents and found an inverse relationship between regional changes in antidepressant prescriptions and suicide rates. Although these data do not imply causality, they undermine the suggestion that antidepressant use strongly contributes to completed suicide.

Third, antidepressants are effective treatments for disorders that frequently complicate pediatric MDD. As reviewed by Geller et al (2003), five SSRIs have clearly been shown to successfully treat pediatric OCD. Similarly, studies of non-OCD anxiety disorders have also demonstrated robust evidence of efficacy for three SSRIs: fluoxetine, fluvoxamine, and paroxetine (Birmaher et al 2003; Research Unit on Pediatric Psychopharmacology Anxiety Study Group 2001; Wagner et al 2004a). Furthermore, a review of data available at the 2004 FDA meeting suggested that newer antidepressants are efficacious treatments for pediatric anxiety disorders (U.S. Food and Drug Administration 2004a).

Finally, although psychotherapeutic treatments might have some benefit, data from the TADS study, which directly compared CBT with medication, indicate that CBT (43%) is inferior to fluoxetine (61%), comparable to placebo (35%), and is most efficacious only when administered concomitantly with fluoxetine. Of interest, however, is the finding that the 43% CBT response rate in the TADS study was lower than the 65% CBT response rate observed in an earlier CBT study of depressed adolescents (Brent et al 1997). Factors such as greater severity, chronicity, and expectancy bias of subjects randomized to the possible medication group might account for these discrepant findings (Bridge and Brent 2004).

Given the significant morbidity associated with pediatric MDD, it is clear that some form of treatment must be recommended. The SSRIs unquestionably have significant limitations, but efficacy data indicate some benefits, with the data seeming to be strongest for fluoxetine. Therefore, in the absence of additional RCTs, SSRIs remain a reasonable first-line treatment for pediatric MDD. Although fluoxetine emerges as the SSRI with the strongest support, it also seems reasonable to use other SSRIs if they have demonstrated clinical benefit or if fluoxetine is not tolerable.

Pathophysiological Factors Influencing Future Directions

Limitations of the current antidepressants reveal the pressing need for developing new treatments. Recent data on the behavioral and neural processes underlying emotional regulation suggest that MDD is mediated by many complex neurophysio-

logic processes involving multiple brain systems and regulatory pathways. Novel therapies that target various pathogenic processes, such as those at the cellular and molecular level, might therefore prove more efficacious than SSRIs, which target the monoamine system.

The predominance of research on the pathophysiology of MDD has focused on adults rather than children. Extrapolating these adult data to research on novel therapies in children is relevant only if pediatric MDD exhibits commonalities with adult MDD; however, if pediatric MDD involves unique pathophysiological processes, a truly novel research approach will be needed. Below, we summarize evidence on the relationship between pediatric and adult MDD and present potentially informative novel therapeutic approaches for pediatric MDD.

Diagnostic Heterogeneity and Developmental Aspects of MDD

Current theories hypothesize that pediatric MDD is a heterogeneous disorder comprising many subtypes that each possess relatively unique symptom profiles, course, risk factors, neurobiology, and treatment response. Potential differences across subtypes therefore raise questions about the specificity of the relationship between pediatric and adult MDD. For example, if a specific subtype of pediatric MDD exhibits a strong association with adult MDD, this subtype might share biological mechanisms of treatment response. In contrast, other subtypes of pediatric MDD might not relate to adult MDD but rather represent early signs of a bipolar diathesis, thereby exhibiting a poor response to antidepressants. Indeed, some data suggest that as many as 20%–40% cases of pediatric MDD might represent initial manifestations of bipolar disorder; these children typically present with very early onset of symptoms, psychomotor retardation or psychosis (Geller et al 1994; Strober and Carlson 1982). These data indicate that understanding treatment response will rely heavily on knowledge of the psychobiological correlates of specific depressive subtypes.

With respect to developmental consistency, clinical and pathophysiological data suggest that pediatric and adult MDD share some common features but also exhibit significant differences. In these studies, pediatric MDD was considered a single syndromal entity, rather than any particular specific depressive subtype. In terms of similarities, data from prospective and family-based studies demonstrate developmental consistency of MDD. Prospective studies indicate that a diagnosis of MDD during adolescence predicts a high risk for recurrent depression during adulthood (Pine et al 1998; Rao et al 1995; Weissman et al 1999). Family studies indicate that MDD aggregates in parents and their child offspring (Hammen et al 1990; Orvaschel et al 1988; Williamson et al 1995). Cognitive similarities are also found in pediatric and adult MDD. For example, both disorders exhibit similar perturbations in information processing, such as memory biases for negative material (Bradley et al 1995; Bishop et al 2004; Gotlib et al 2004a, 2004b; Neshat-Doost et al 1998).

Despite the similarities, there is considerable evidence indicating that pediatric and adult MDD differ in their biological correlates, as well as their response to antidepressants. For example, adult MDD but not pediatric MDD is associated with specific signs of hyperactivity in the hypothalamic–pituitary–adrenal (HPA) axis, such as an abnormal response to corticotropin-releasing factor (CRF) challenge (Birmaher et al 1996; Dorn et al 1996; Plotsky et al 1998). Similarly, serotonin challenge studies demonstrate signs of reduced activity in raphe neurons in adults but enhanced activity in children (Birmaher et al 1997;

Ryan et al 1992). Finally, differences in cellular immunity and sleep-related variables also differentiate child and adult MDD (Kaufman et al 2001). Therefore, despite data supporting developmental consistency of MDD, the psychobiological mechanisms underlying the illness might differ across development. As such, hypotheses on adult pathophysiology cannot necessarily be applied to children.

A number of pathophysiological models can potentially explain the conflicting data on the relationship between pediatric and adult MDD. For example, pediatric MDD might represent a developmental manifestation of a common core illness process underlying some forms of MDD that manifest in both childhood and adulthood. Biological correlates of this illness might change in tandem with development. Another possibility is that pediatric and adult MDD might represent distinct subtypes or classes of a larger family of disorders, all of which arise from distinct pathophysiological processes that lead to a final common pathway. Elucidating these models will require studies that investigate the correlates of depression across the lifespan. Methodological strategies for conducting such research include 1) using functional neuroimaging methods to compare neural responses to similar activation paradigms in children, adolescents, and adults; 2) designing prospective studies that assess neural, cognitive, and physiological function across development; and 3) recruiting subjects at a similar stage of illness (i.e., initial vs. recurrent onset) (Kaufman et al 2001).

Developmental Psychobiology and Treatment Response

There are virtually no studies of pediatric MDD that provide insights into the psychobiological factors contributing to the heterogeneity in treatment response. Similarly, studies of adult MDD also fail to identify any psychobiological correlates that are clinically useful in predicting treatment response. Nevertheless, four specific heuristics based on psychobiological studies in adult MDD might provide insights for future treatment studies of pediatric MDD. These heuristics include data on MDD subtypes, deficits in reward function and threat detection, HPA axis dysfunction, and information-processing biases.

First, some clinical work defining subtypes of adult MDD seems promising. Perhaps the strongest data arise from studies demonstrating psychobiological differences between atypical and melancholic MDD, including differential antidepressant treatment responses (Gold and Chrousos 1999; Fountoulakis et al 2004). Atypical depression can further be dissected into discrete subtypes according to course and psychobiology (Stewart et al 2002, 2003). In terms of developmental perspectives, some work suggests that pediatric MDD might show stronger relationships to atypical as opposed to melancholic MDD (Stewart et al 2003; Williamson et al 2000). The degree of atypical features in pediatric MDD, however, has not exhibited a strong relationship to treatment outcome. More direct assessment of these psychobiological processes might identify subtypes of adult and pediatric MDD that exhibit unique responses to specific treatments.

Second, data from animal models of hedonic regulation and threat detection reveal recruitment of neural circuits encompassing the prefrontal cortex (PFC), medial temporal lobe, and striatum in these processes. In fact, MDD might be characterized by deficits in two overlapping neural circuits: a “fear” circuit that is involved in regulation of the threat response and encompasses the amygdala, hippocampus, and associated PFC regions (LeDoux 2003); and a “reward” circuit that is involved in the regulation of reward-related behavior and encompasses the striatum and PFC (Bressan and Crippa 2005).

Translational methods have extended these basic science findings to adult MDD. Thus, both postmortem and neuroimaging studies of depressed adults consistently report abnormalities in structural and functional aspects of circuits involving the amygdala and prefrontal cortex (Drevets 2003). Moreover, these neural abnormalities have been linked to disruptions in serotonergic regulation and therefore might relate to treatment response (Hariri et al 2002; Pezawas et al 2005). It remains unclear, however, how abnormalities in hedonic regulation and threat detection fit within a larger coherent developmental pathophysiological framework. Furthermore, translational research in adult MDD remains quite removed from clinical care. Future work might identify distinct and clinically meaningful subtypes of MDD on the basis of distinct patterns of neural circuitry perturbation. Consistent with this possibility, changes in PFC structure and function have been correlated with some clinical features in adult MDD, such as the degree of melancholic as opposed to atypical features, family history profiles, or age of onset (Drevets 2003; Fountoulakis et al 2004). To date, few studies have examined the degree to which neural circuit dysfunction correlates with specific pediatric MDD subtypes.

Third, research examining the effects of stress on behavior and brain function in animal models provides further insights regarding potential MDD subtypes and consequently treatment response. The strongest data on stress-related developmental changes in neural function emerge from animal studies of the threat response. Research in both rodents and nonhuman primates demonstrates that environmental manipulations have a unique capacity to shape fear behavior early in development (Francis et al 1999; Gross and Hen 2004; Heim and Nemeroff 1999; Ladd et al 2000). Some of these changes might be mediated through gene–environment interactions operating during development. For example, genetic manipulations in rodents demonstrate a developmentally sensitive period during which serotonergic genes have the unique capacity to shape threat response behavior. Thus, basic science data suggest that the fear circuit of immature mammals is more sensitive to adverse influences than that of mature mammals. These data raise questions regarding the differential impact of SSRIs on fear circuitry across human development.

In humans, stress-related perturbations in HPA axis function are associated with MDD pathophysiology. Specifically, Heim et al (2000, 2001) found that one particular subtype of adult MDD, which is associated with a history of childhood abuse, is characterized by an enhanced cortisol response. Moreover, Nemeroff et al (2004) suggest that the unique subtype of adult MDD associated with stress exposure during development exhibits a particularly robust response to psychotherapy as opposed to antidepressants. Research on stress-related perturbations in the HPA axis also relate to the melancholic–atypical distinction, with some evidence documenting divergent HPA axis perturbations in the two subtypes (Gold and Chrousos 1999).

Given the developmental focus of this work, research on stress–dysfunction could carry profound implications for prevention and treatment of pediatric MDD. Nevertheless, much of the work in humans remains retrospective, and studies in children have not always generated findings comparable to those from studies in adults. For example, although the findings of Nemeroff et al (2004) show a significantly better response to psychotherapy than to antidepressants in depressed adults with a history of childhood abuse, pediatric MDD with a history of abuse exhibits a poor psychotherapeutic response (Brent 2004). Prospective studies are needed to define the degree to which perturbed

psychobiological processes in children relate to MDD subtypes and treatment response in adults.

A final body of work examines information processing biases in adult MDD and the degree to which these psychological processes relate to psychobiology and treatment response. In general, research in this area suggests that unique subtypes of MDD can be defined according to their distinct patterns of abnormal information processing, as manifested on tests of attention, memory, or other psychological processes (Gotlib et al 2004a, 2004b; Rinck and Becker 2005). Work in this area varies in terms of the degree to which perturbed processes are broadly or precisely defined. For example, narrowly defined biases in mnemonic processes might relate to unique subtypes of adult MDD that respond to specific cognitive interventions; however, this work has generally not informed conceptualizations of pharmacotherapeutics. Alternatively, data from Bruder et al (2004) demonstrate more broad perturbations in information processing that are based on patterns of hemispheric specialization; these perturbations might predict antidepressant response profiles. For example, signs of left hemispheric dysfunction in adult MDD seem to predict selective response to fluoxetine (Bruder et al 2001), whereas signs of right hemisphere dysfunction seem to predict response to tricyclics (Bruder et al 1990; Stewart et al 1999). These hypotheses have only recently been extrapolated to pediatric MDD (Kentgen et al 2000; Pine et al 2000).

Use of Novel Treatments in Pediatric MDD

The delineation of neural circuitry in adult MDD has stimulated interest in research on novel therapeutic agents. For example, research on HPA axis perturbations in adult MDD implicates overactivity in neurons expressing CRF as a potential cause of MDD (Plotsky et al 1998). On the basis of this view, CRF antagonists and related peptidergic agents are thought to represent viable novel antidepressant agents. Similarly, adult MDD has been conceptualized as arising from abnormalities in neural plasticity involving the fear circuit. On the basis of this view, a series of agents that modulate plasticity have been hypothesized to possess antidepressant properties. For example, glutamate dysfunction might give rise to aberrant neuroplastic interactions between frontal and temporal brain regions involved in stress adaptation (Zarate et al 2002). Agents, such as riluzole, that attenuate glutamate activity might possess antidepressant properties through their effects on neuroplasticity (Zarate et al 2005).

The appropriateness of using such agents in studies of pediatric MDD raises complex ethical questions. Fost (2001) provides one of the few ethical reviews on this specific topic. The prevailing convention has been to restrict research on novel therapeutics to child populations with highly treatment-resistant forms of psychiatric illness and to use experimental treatments only after they have demonstrated success in adults. This policy carries clear benefits and risks. In terms of benefits, the policy provides some degree of assurance that treatments with a relatively high chance of success will receive priority for research. Moreover, the policy also protects a vulnerable population against unanticipated adverse events, which presumably would have occurred in adults. On the other hand, given evidence of developmental plasticity in the fear circuit and its relationship to MDD, it remains unclear whether adult data can predict efficacy or safety in children. One could therefore argue in favor of conducting therapeutic studies in children even before a treatment has been shown to be of benefit in adults. This

clearly would represent a novel approach that has yet to be pursued and would therefore require thoughtful consideration.

Conclusions

The present report reviews recent data on the pharmacology of pediatric MDD. Three general conclusions emerge. First, existing data support the use of fluoxetine as a first-line treatment. Second, despite their modest efficacy profile, other SSRIs seem to be reasonable treatment options as well, particularly for patients who fail to respond to an initial trial of fluoxetine with or without CBT. Third, there is a striking paucity of safe and effective treatments for pediatric depression, and major attention to this problem is needed.

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